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EXAMINER	
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ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/806,370	YONGHONG ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/23/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *alignment*.

DETAILED ACTION

Status of the Application

Claims 31-39 are pending.

Applicant's preliminary amendment canceling claims 1-30 and 40-73 as submitted on 3/23/2004 is acknowledged.

Claims 31-39 are directed to a method of screening for agents that regulate the activity of a human transmembrane serine protease. An action on the merits follows.

Specification

1. The specification is objected to for the following reasons. The preliminary amendment filed 3/23/2004 contains references to prior applications which lack their current status. Appropriate correction is required.

2. The specification is objected to for the following reasons. The preliminary amendment filed 3/23/2004 contains a reference to PCT/EP01/06618 (filed 6/12/2001) as a copending application to which priority is claimed. However, the Examiner has been unable to find evidence that shows PCT/EP01/06618, which was filed 6/12/2001, to be copending at the time of filing of the instant application, which is 3/23/2004. Thus, it appears that a priority claim to PCT/EP01/06618 is improper. In addition, there is no indication as to whether Applicant is claiming domestic or foreign priority. It is noted that neither the oath nor the ADS recite any priority claim to PCT/EP01/06618. Correction/clarification is required.

Priority

3. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 119(e) to provisional application No. 60/211,224 filed on 06/13/2000, 60/283,353 filed on 04/13/2001, and 60/283,648 filed on 04/16/2001.

4. US provisional application No. 60/211,224 filed on 06/13/2000 appears to disclose and claim the method of the instant application.

5. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 120 or 121 to US application No. 09/879,792 filed on 06/13/2001.

6. Acknowledgment is made of a claim for priority to PCT/EP01/06618 filed on 6/12/2001. However, as indicated above, there is no indication in the specification, the oath or the ADS filed on 3/23/2004 as to whether the claimed priority is domestic or foreign. It is also noted that parent application 09/879,792 does not claim priority to PCT/EP01/06618. Thus, for the instant application to claim priority to PCT/EP01/06618 under 35 U.S.C. 120 or 121, Applicant is required to show copendency between the instant application and PCT/EP01/06618. A claim for priority under 35 U.S.C. 119(a)-(d) cannot be based on PCT/EP01/06618, since the instant United States application was filed more than twelve months thereafter.

Information Disclosure Statement

7. The information disclosure statement (IDS) submitted on 3/23/2004 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Drawings

8. The drawings submitted 3/23/2004 have been reviewed and are accepted by the Examiner.

Claim Rejections - 35 USC § 112, Second Paragraph

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 31-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claim 31 (claims 32-39 dependent thereon) is indefinite in the recitation of "agents that can regulate an activity of a human transmembrane serine protease.....amino acid sequence selected from the group consisting of .....and (c) biologically active variants thereof" for the following reasons. The term "an activity of a human transmembrane serine protease" is unclear and confusing because the term "an activity" implies more than one activity. Thus, one cannot determine whether the intended activity is the enzymatic activity (i.e., serine protease) or if another unknown activity is intended. The term "biologically active" is also unclear and confusing because the term can have many different interpretations to one of skill in the art. For example, one interpretation of the term "biologically active" in regard to polypeptides is the ability to elicit antibodies. In addition, the term "biologically active variants thereof" is unclear because while the claim in the preamble refers to (c) as an amino acid sequence (i.e., "contacting a test compound with a polypeptide comprising an amino acid sequence selected from the group consisting of (a)..., (b)...., and (c)..."), the item recited in (c) is not a sequence but a biologically active variant. In addition, the term "thereof" is unclear and confusing because one cannot determine if the term "thereof" refers to (a) and (b), (a), or (b). For examination purposes, it will be assumed that the claim is directed to a method of screening for agents that can regulate the enzymatic activity of a human transmembrane serine protease, comprising the steps of contacting a test compound with a polypeptide comprising an amino acid sequence selected from the group consisting of (a) the amino acid sequence of SEQ ID NO: 12, (b) the amino acid sequence encoded by the cDNA insert

contained within plasmid pCRII-TMSP3 (ATCC PTA-3433, and (c) the amino acid sequence of any human transmembrane serine protease. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 31-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 31-32, 34-39 (as interpreted) are directed in part to an *in vivo* method of screening for agents that can regulate the enzymatic activity of any human transmembrane serine protease. Claim 33 (as interpreted) is directed in part to an *in vitro* method of screening for agents that can regulate the enzymatic activity of any human transmembrane serine protease. See Claim Rejections under 35 USC 112, second paragraph, for claim interpretation.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed

correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

There is no structural limitation with regard to the members of the genus of human transmembrane serine proteases required by the claimed method. In addition, there is no limitation as to whether the method is carried out *in vivo* or *in vitro* (except in claim 33). While the specification in the instant application discloses the structure of one species of the genus of enzymes recited (SEQ ID NO: 12), it provides no information as to the structural elements required in any human transmembrane serine protease, nor does it teach which structural elements of the polypeptide of SEQ ID NO: 12 are required to display serine protease activity. Also, there is no disclosure of the structural elements required in a human transmembrane serine protease which are not found in other serine proteases. There is absolutely no teaching or disclosure describing practicing the claimed method *in vivo*. The specification fails to describe any additional species by any relevant, identifying characteristics or properties other than by functionality (i.e., serine protease activity).

The claims encompass a large genus of proteins which are structurally unrelated. A sufficient written description of a genus of proteins may be achieved by a recitation of a representative number of proteins defined by their amino acid sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. However, in the instant case, there is no structural feature which is representative of all the members of the genus of serine proteases recited in the claims, and there is no information as to a correlation between structure and function. Furthermore, while one could argue that SEQ ID NO: 12 is representative of the structure of all the members of the genus of proteins recited, such that the recited genus is adequately described by the disclosure of SEQ ID

NO: 12, it is noted that the art teaches several examples of how even small changes in structure can lead to changes in function. For example, Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one conservative amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Therefore, since minor structural changes may result in changes affecting function, and no additional information correlating structure with serine protease activity has been provided, one cannot reasonably conclude that the structures disclosed are representative of all the enzymes recited.

Due to the fact that the specification only discloses one species of the genus of human transmembrane serine proteases (i.e., SEQ ID NO: 12), as well as the lack of description of any additional species by any relevant, identifying characteristics or properties, one of skill in the art would not recognize from the disclosure that Applicant was in possession of the claimed invention.

14. Claims 31-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention appears to employ a novel vector (i.e., plasmid pCRII-TMSP3). Since the vector is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The recited plasmid sequence is not fully disclosed, nor have all the sequences required for its construction been shown to be publicly known and freely available. The enablement requirements of 35 U.S.C. §112 may be satisfied by a deposit of the plasmid. The specification does not disclose a repeatable process to obtain the vector and it is not apparent if the DNA sequence is

readily available to the public. Accordingly, it is deemed that a deposit of this plasmid should have been made in accordance with 37 CFR 1.801-1.809.

It is noted that Applicant has deposited the plasmid (page 95, fifth complete paragraph) but there is no indication in the specification as to public availability. If the deposit was made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific plasmid has been deposited under the Budapest Treaty and that the plasmid will be available to the public under the conditions specified in 37 CFR 1.808, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance or compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

a. during the pendency of this application , access to the invention will be afforded to the Commissioner upon request;

b. upon granting of the patent the plasmid will be available to the public under the conditions specified in 37 CFR 1.808;

c. the deposit will be maintained in a public repository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and

d. the deposit will be replaced if it should ever become non-viable.

15. Claims 31-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method of screening for agents that can regulate the enzymatic activity of (1) the polypeptide of SEQ ID NO: 12, or (2) fragments of the polypeptide of SEQ ID NO: 12 having serine protease activity, does not reasonably provide enablement for an *in vivo* method of screening for agents that can regulate the enzymatic activity of (1) the polypeptide of SEQ ID NO: 12, or (2) any human transmembrane serine protease. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2nd 1400 (Fed. Cir. 1988)) as follows: (1) quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence and absence of working examples, (4) the nature of the invention, (5) the state of prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breath of the claims. The factors which have lead the Examiner to conclude that the specification fails to teach how to make and/or use the claimed invention without undue experimentation, are addressed in detail below.

The breath of the claims. Claims 31-39 are so broad as to encompass (1) an *in vivo* method of screening for agents that can regulate the enzymatic activity of (i) the polypeptide of SEQ ID NO: 12, or (ii) any human transmembrane serine protease, and (2) an *in vitro* method of screening for agents that can regulate the enzymatic activity of any human transmembrane serine protease. See Claim Rejections under 35 USC 112, second paragraph, for claim interpretation. The enablement provided is not commensurate in scope with the claims due to the potentially large number of enzymes of unknown structure recited in the claims as well as the lack of information regarding how to practice the claimed method *in vivo*. In the instant case, the specification enables an *in vitro* method of screening for agents that can regulate the enzymatic activity of (1) the polypeptide of SEQ ID NO: 12, or (2) fragments of the polypeptide of SEQ ID NO: 12 having serine protease activity.

The amount of direction or guidance presented and the existence of working examples. The specification discloses the amino acid sequences of a single human transmembrane serine protease (SEQ ID NO: 12). However, the specification fails to provide any clue as to (1) the structural elements required in any human transmembrane serine protease, or (2) how to practice the claimed method *in vivo*. No correlation between structure and serine protease activity has been presented. There is no information or

guidance as to the amino acids in the polypeptide of SEQ ID NO: 12 which are associated with the recited enzymatic activity, which amino acid residues in the polypeptide of SEQ ID NO: 12 can be modified and which ones are to be conserved to create a variant displaying the same activity as that of the polypeptide of SEQ ID NO: 12. No information has been provided which describes how one of skill in the art can screen for agents that regulate the enzymatic activity of a human transmembrane serine protease *in vivo*. If the testing is carried out in a transgenic animal able to produce the human transmembrane serine protease, the specification fails to disclose working examples or specific methods showing a transgenic animal capable of producing the human transmembrane serine protease, how to ensure that any effect in the human transmembrane serine protease is the direct result of the compound tested, or how to ensure that the compound tested is not metabolized prior to its contact with the human transmembrane protease recited. Similarly, if the testing is carried out in a human being, the specification is silent with regard to how to ensure that any effect in the human transmembrane serine protease is the direct result of the compound tested, or how to ensure that the compound tested is not metabolized prior to its contact with the human transmembrane protease recited. In addition, the specification is completely silent with regard to how to deliver and obtain expression of the nucleic acid encoding the polypeptide of SEQ ID NO: 12 in a human being.

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art. The sequence of a protein determines the structural and functional properties of that protein. In the instant case, neither the specification nor the art provide a correlation between structure and activity such that one of skill in the art can envision the structure of any human transmembrane serine protease, or any naturally-occurring variant of the polypeptide of SEQ ID NO: 12 having enzymatic activity. In addition, the art does not provide any teaching or guidance as to (1) which amino acids in the polypeptide of SEQ ID NO: 12 can be modified and which ones are conserved such that one of skill in the art can make variants as recited with the same biological activity as that of the

polypeptide of SEQ ID NO: 12, (2) which segments of the polypeptide of SEQ ID NO: 12 are essential for activity, and (3) the general tolerance of serine proteases to structural modifications and the extent of such tolerance. The art clearly teaches that changes in a protein's amino acid sequence to obtain the desired activity without any guidance/knowledge as to which amino acids in a protein are required for that activity is highly unpredictable. At the time of the invention there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (Introduction to Protein Structure, Garland Publishing Inc., New York, page 247, 1991) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing *de novo* stable proteins with specific functions. The teachings of Branden et al. are further supported by the teachings of Witkowski et al. (Biochemistry 38:11643-11650, 1999) and Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) already discussed above, where it is shown that even small amino acid changes result in enzymatic activity changes.

With regard to the production of transgenic animals, the prior art teaches that making genetically modified animals is highly unpredictable. The relevant art has for many years indicated that the unpredictability of generating transgenic animals lies with the site or sites of integration of the transgene into the target genome. Kappel et al. (Current Opinion in Biotechnology 3:548-553, 1992) teach that transgenic animals are known to have inherent cellular mechanisms which may alter the pattern of gene expression, such as DNA methylation or deletion from the genome (page 549, right column, third paragraph). Furthermore, Mullins et al. (Hypertension 22(4):630-633, 1993) teach that integration of a transgene in different species may result in widely different phenotypic responses (page 631, left column, first paragraph, last sentence). Also, Mullins et al. (J. Clin. Invest. 97(7):1557-1560, 1996) teach that "the

use of nonmurine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to another." (page 1559, Summary). Wigley et al. (Reprod. Fert. Dev. 6:585-588, 1994) indicate that transgenesis by microinjection has a number of limitations including random integration in the genome and integration of transgenes in multiple copies at one site such that expression level is not proportional to transgene copy number (page 585, Introduction). Cameron (Molecular Biotechnology 7:253-265, 1997) teaches that well-regulated expression of the transgene is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (page 256, left column, last three lines, right column, first three lines). According to Cameron, transgene expression with different transgenic lines produced with the same constructs is unpredictable and expression levels do not correlate with the number of transgene copies integrated, thus indicating the influence of the integration site on the expression pattern (page 256, right column, lines 3-13).

In regard to DNA delivery and expression in human tissues, the art teaches the high unpredictability of delivering DNA to human tissues and achieving the desired expression. For example, Phillips (J. Pharm. Pharmacology 53:1169-1174, 2001) teaches that the major challenges in gene therapy have been delivery of DNA to target cells and duration of expression (Abstract). According to Phillips, the problem regarding gene therapy is twofold in that (1) a system must be design to deliver DNA to a specific target while preventing degradation within the body, and (2) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for a determined amount of time (page 1170, left column, lines 7-15). Gardlik et al. (Med. Sci. Monit. 11(4):RA110-121, 2005) teach that (1) while there are a number of methods known for delivery of DNA, there is no clear ideal delivery system (RA119, last paragraph), and (2) the main problem in gene therapy lies in the secure and efficient delivery of genes into target cells and tissues (RA110, Summary).

The quantity of experimentation required to practice the claimed invention based on the teachings of the specification. While methods of generating or isolating variants of a protein were known in the art at the time of the invention, it was not routine in the art to screen by a trial and error process for the extremely large number of proteins found in a human being to determine which ones are transmembrane serine proteases. Furthermore, it is not routine in the art to isolate/create any protein with the activity recited without any knowledge as to the structural features which would correlate with that activity. In the absence of (1) a rational and predictable scheme for modifying any amino in the polypeptide SEQ ID NO: 12 such that the resulting protein is a serine protease activity, and/or (2) a correlation between structure and serine protease activity, one of skill in the art would have to test an essentially infinite number of proteins to determine which ones have serine protease activity.

While enzymatic assays are well known in the art, and the skilled artisan can produce variants of the polypeptide of SEQ ID NO: 12, the amount of experimentation required is not routine due to the fact that the number of species to be tested extremely large. Therefore, while enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, as is the case herein, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed so that a reasonable number of species can be selected for testing. In view of the fact that such guidance has not been provided in the instant specification, it would require undue experimentation to enable the full scope of the claims.

Furthermore, given the teachings of the art regarding the differences in expression of a transgene in different species, the limitations regarding the integration and expression of a transgene, the unpredictability of delivering and expressing DNA in human tissues, and in view of the lack of guidance provided by the specification, it would have required undue experimentation to engineer any transgenic animal to produce the polypeptide of SEQ ID NO: 12, or any human transmembrane serine protease.

Therefore, taking into consideration the extremely broad scope of the claims, the lack of guidance, the amount of information provided, the lack of knowledge about a correlation between structure and function, the high degree of unpredictability of the prior art in regard to (a) structural changes and their effect on function, (b) generation of transgenic multicellular organisms, and (c) delivery and expression of DNA in human tissues, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

17. Claims 31-33, 35-37 rejected under 35 U.S.C. 102(a) as being anticipated by Morser et al. (WO 99/64608, published 12/16/1999; cited in the IDS).

Claims 31 and 33 are directed in part to an *in vitro* method of screening for agents that can regulate the enzymatic activity of a human transmembrane serine protease, wherein said method requires detecting binding of the test compound with the serine protease. Claims 32 and 35 are directed to the method of claim 31, wherein the serine protease used in the method is either in a cell or lacking cellular components, respectively. Claims 36-37 are directed to the method of claim 31, wherein either the serine protease or the test compound have a detectable label. See Claim Rejections under 35 USC 112, second paragraph for claim interpretation.

Morser et al. teach a human transmembrane serine protease (corin; SEQ ID NO: 1/2; page 2, lines 8-11; page 6, lines 3-12) and a method for identifying modulators of the serine protease (page 24, line 26-page 7, line 2) and a method for identifying compounds which bind to the serine protease (page 25, lines 21-29). The serine protease of the disclosed method can be used in combination with immunoglobulin domains as a fusion protein. Immunoglobulin domains are known detectable labels in the art. Morser et al. also teach that the serine protease can be used in the reaction mixture as substantially purified or as a component of a cell (page 26, lines 1-2). Morser et al. teach antibodies to the serine protease which are agents that bind to the serine protease and discloses that the serine protease and corresponding antibodies can be labeled for a detectable signal (page 30, line 30-page 31-line 5). Thus, the teachings of Morser et al. anticipate the instant claims as written.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

20. Claims 38-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morser et al. (WO 99/64608, published 12/16/1999; cited in the IDS) in view of Bandman et al. (U.S. Patent No. 5925521, issued 7/20/1999). The teachings of Morser et al. have been discussed above. Morser et al. do not teach a method wherein the test compound or the serine protease are bound to a solid support. Bandman et al. teach a human serine carboxypeptidase (protease) and a method to screen for compounds which would bind to the serine carboxypeptidase (column 17, lines 25-30), wherein the serine carboxypeptidase is affixed to a solid support (column 25, lines 57-65), or the compounds are attached to a solid substrate (column 25, line 66-column 26, line 6).

Claims 38-39 are directed to the method of claim 31 as described above wherein either the test compound or the serine protease are bound to a solid support.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to practice the method of Morser et al. with either the test compound or the serine protease attached to a solid support. A person of ordinary skill in the art is motivated to practice the method of Morser et al. with either the test compound or the serine protease attached to a solid support for the benefit of faster and easier detection. Immobilization would allow for high throughput screening of compounds having suitable binding affinity to the protein of interest. One of ordinary skill in the art has a reasonable expectation of success at attaching either the test compound or the serine protease to a solid support since Bandman et al. teach a method for screening test compounds which would bind to the carboxypeptidase wherein either the enzyme or the test compound is bound to a solid surface. In addition, immobilization of compounds/enzymes to solid supports is well known and widely used in the art. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

21. Claims 31-33, 35-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. (Biochimica et Biophysica Acta 1518:204-209; cited in the IDS) in view of Morser et al. (WO 99/64608, published 12/16/1999; cited in the IDS) and further in view of Bandman et al. (U.S. Patent No. 5925521, issued 7/20/1999). The teachings of Morser et al. and Bandman et al. have been discussed above. Kim et al. teach a human transmembrane serine protease which is 98.4% sequence identical to the polypeptide of SEQ ID NO: 12 (98.4% = 553x100/562). Kim et al. do not teach a method of screening for agents that bind to the human transmembrane serine protease.

Claims 31 and 33 are directed in part to an *in vitro* method of screening for agents that can regulate the enzymatic activity of a human transmembrane serine protease, wherein said method requires detecting binding of the test compound with the serine protease. Claims 32 and 35 are directed to the method of claim 31, wherein the serine protease used in the method is either in a cell or lacking cellular components, respectively. Claims 36-37 are directed to the method of claim 31, wherein either the serine protease or the test compound have a detectable label. Claims 38-39 are directed to the method of claim 31 as described above wherein either the test compound or the serine protease are bound to a solid support. See Claim Rejections under 35 USC 112, second paragraph for claim interpretation.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method of Morser et al. and Bandman et al. with the human transmembrane serine protease of Kim et al. A person of ordinary skill in the art is motivated to practice the method of Morser et al. and Bandman et al. with the polypeptide of Kim et al. for the benefit of further characterizing the serine protease. One of ordinary skill in the art has a reasonable expectation of success at practicing the method of Morser et al. and Bandman et al. since Morser et al. and Bandman et al. disclose a similar method with a different human transmembrane serine protease. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

Allowable Subject Matter

22. An *in vitro* method of screening for agents that can regulate the enzymatic activity of the human transmembrane serine protease of SEQ ID NO: 12, wherein the method comprises the steps of (1) contacting a test compound with the polypeptide of SEQ ID NO: 12, and (2) detecting binding of the polypeptide of SEQ ID NO: 12 with the test compound, wherein a test compound that binds the polypeptide of SEQ ID NO: 12 is identified as a potential agent for regulating the enzymatic activity of the polypeptide of SEQ ID NO: 12 appears to be allowable over the prior art of record.

Conclusion

23. No claim is in condition for allowance.

24. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
November 7, 2006

GenCore version 5.1.9

OM protein - protein search, using sw model

Run on: July 26, 2006, 21:45:17 ; Search time 301 Seconds
(without alignments)
1727.106 Million cell updates/sec

Title: US-10-806-370-12
Perfect score: 2999
Sequence: 1 MERDSHGNASPARTPSAGAS.....TEVLPWIYSKMESEVRFRKS 562

Scoring table: BLOSUM62
Gapop 10.0 , Gapext 0.5

Searched: 2849598 seqs, 925015592 residues

Total number of hits satisfying chosen parameters: 2849598

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

Database : UniProt_7.2:*
1: uniprot_sprot:*
2: uniprot_trembl:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	2956	98.6	581	1	TMPSD_HUMAN	Q9bye2 homo sapien
2	2510.5	83.7	543	1	TMPSD_MOUSE	Q5u405 mus musculu
3	891	29.7	359	2	Q4SPG0_TETNG	Q4spg0 tetraodon n
4	777.5	25.9	490	1	TMPS2_MOUSE	Q9jiq8 mus musculu
5	771.5	25.7	490	2	Q3UKE3_MOUSE	Q3uke3 mus musculu
6	770.5	25.7	490	2	Q7TN04_MOUSE	Q7tn04 mus musculu
7	769.5	25.7	490	2	Q6P7D7_RAT	Q6p7d7 rattus norv
8	763.5	25.5	453	2	Q812A6_MOUSE	Q812a6 mus musculu
9	763.5	25.5	475	2	Q3TZ06_MOUSE	Q3tz06 mus musculu
10	763.5	25.5	490	2	Q920K3_RAT	Q920k3 rattus norv
11	762.5	25.4	453	1	TMPS3_MOUSE	Q8k1t0 mus musculu
12	762.5	25.4	453	2	Q2M1G4_MOUSE	Q2m1g4 mus musculu
13	761.5	25.4	484	2	Q3I1U4_MACMU	Q3i1u4 macaca mula
14	759.5	25.3	486	2	Q5PRA6_BRARE	Q5pra6 brachydanio
15	755	25.2	484	2	Q3I1V4_PANPA	Q3i1v4 pan paniscu
16	754	25.1	484	2	Q3I1V3_9PRIM	Q3i1v3 gorilla gor
17	751	25.0	484	2	Q3I1V5_PANTR	Q3i1v5 pan troglod
18	744	24.8	484	2	Q3I1U8_HYLSY	Q3i1u8 hylobates s
19	740.5	24.7	492	2	Q6GTK7_HUMAN	Q6gtk7 homo sapien
20	738.5	24.6	492	1	TMPS2_HUMAN	O15393 homo sapien
21	738.5	24.6	492	2	Q96T73_HUMAN	Q96t73 homo sapien
22	736.5	24.6	538	2	Q5USC7_HUMAN	Q5usc7 homo sapien
23	731	24.4	454	1	TMPS3_HUMAN	P57727 homo sapien
24	713.5	23.8	722	2	Q6NUF5_XENLA	Q6nuf5 xenopus lae
25	712.5	23.8	767	2	Q9DGR2_XENLA	Q9dgr2 xenopus lae
26	697.5	23.3	437	1	TMPS4_HUMAN	Q9nrs4 homo sapien
27	696	23.2	445	2	Q8CJ17_RAT	Q8cj17 rattus norv
28	689.5	23.0	439	2	Q5RDX7_PONPY	Q5rdx7 pongo pygma
29	684.5	22.8	435	1	TMPS4_MOUSE	Q8vca5 mus musculu
30	684	22.8	388	2	Q4RRR7_TETNG	Q4rrr7 tetraodon n
31	668.5	22.3	371	2	Q8CJ16_RAT	Q8cj16 rattus norv
32	664	22.1	455	1	TMPS5_MOUSE	Q9er04 mus musculu
33	659	22.0	455	2	Q8CDR0_MOUSE	Q8cdr0 mus musculu
34	644.5	21.5	457	1	TMPS5_HUMAN	Q9h3s3 homo sapien
35	616.5	20.6	445	2	Q3U0U6_MOUSE	Q3u0u6 mus musculu
36	611.5	20.4	417	1	HEPS_HUMAN	P05981 homo sapien
37	609.5	20.3	417	2	Q5R5E8_PONPY	Q5r5e8 pongo pygma
38	608.5	20.3	436	1	HEPS_MOUSE	O35453 mus musculu
39	600	20.0	326	2	Q7ZZ80_BRARE	Q7zz80 brachydanio
40	592.5	19.8	416	1	HEPS_RAT	Q05511 rattus norv
41	580.5	19.4	730	2	Q4RHT0_TETNG	Q4rht0 tetraodon n
42	578.5	19.3	572	1	TMPS7_MOUSE	Q8bik6 mus musculu
43	578	19.3	799	1	TMPS6_MOUSE	Q9dbi0 mus musculu
44	578	19.3	799	2	Q6PF94_MOUSE	Q6pf94 mus musculu
45	578	19.3	811	2	Q3KN88_MOUSE	Q3kn88 mus musculu

ALIGNMENTS

```
RESULT 1
TMPSD_HUMAN
ID   TMPSD_HUMAN     STANDARD;      PRT;   581 AA.
AC   Q9BYE2; Q86YM4; Q96JY8; Q9BYE1;
DT   15-MAR-2005, integrated into UniProtKB/Swiss-Prot.
DT   15-MAR-2005, sequence version 2.
DT   07-MAR-2006, entry version 29.
DE   Transmembrane protease, serine 13 (EC 3.4.21.-) (Mosaic serine
DE   protease) (Membrane-type mosaic serine protease).
GN   Name=TMPRSS13; Synonyms=MSP, TMPRSS11;
OS   Homo sapiens (Human).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Euarchontoglires; Primates; Catarrhini; Hominidae;
OC   Homo.
OX   NCBI_TaxID=9606;
RN   [1]
RP   NUCLEOTIDE SEQUENCE [MRNA] (ISOFORMS 1 AND 3), AND TISSUE SPECIFICITY.
RC   TISSUE=Lung;
RX   MEDLINE=21167393; PubMed=11267681; DOI=10.1016/S0167-4781(01)00184-1;
RA   Kim D.R., Sharmin S., Inoue M., Kido H.;
RT   "Cloning and expression of novel mosaic serine proteases with and
RT   without a transmembrane domain from human lung.";
RL   Biochim. Biophys. Acta 1518:204-209(2001).
RN   [2]
RP   NUCLEOTIDE SEQUENCE [MRNA] (ISOFORM 2).
RA   Park T.J., Park W.J.;
RT   "Homo sapiens transmembrane protease, serine 6 (TMPRSS6) mRNA.";
RL   Submitted (DEC-2002) to the EMBL/GenBank/DDBJ databases.
RN   [3]
RP   NUCLEOTIDE SEQUENCE [LARGE SCALE MRNA] (ISOFORM 4).
RC   TISSUE=Placenta;
RX   PubMed=14702039; DOI=10.1038/ng1285;
RA   Ota T., Suzuki Y., Nishikawa T., Otsuki T., Sugiyama T., Irie R.,
RA   Wakamatsu A., Hayashi K., Sato H., Nagai K., Kimura K., Makita H.,
RA   Sekine M., Obayashi M., Nishi T., Shibahara T., Tanaka T., Ishii S.,
RA   Yamamoto J., Saito K., Kawai Y., Isono Y., Nakamura Y., Nagahari K.,
RA   Murakami K., Yasuda T., Iwayanagi T., Wagatsuma M., Shiratori A.,
RA   Sudo H., Hosoiri T., Kaku Y., Kodaira H., Kondo H., Sugawara M.,
RA   Takahashi M., Kanda K., Yokoi T., Furuya T., Kikkawa E., Omura Y.,
RA   Abe K., Kamihara K., Katsuta N., Sato K., Tanikawa M., Yamazaki M.,
RA   Ninomiya K., Ishibashi T., Yamashita H., Murakawa K., Fujimori K.,
RA   Tanai H., Kimata M., Watanabe M., Hiraoka S., Chiba Y., Ishida S.,
RA   Ono Y., Takiguchi S., Watanabe S., Yosida M., Hotuta T., Kusano J.,
RA   Kanehori K., Takahashi-Fujii A., Hara H., Tanase T.-O., Nomura Y.,
RA   Togiya S., Komai F., Hara R., Takeuchi K., Arita M., Imose N.,
RA   Musashino K., Yuuki H., Oshima A., Sasaki N., Aotsuka S.,
RA   Yoshikawa Y., Matsunawa H., Ichihara T., Shiohata N., Sano S.,
RA   Moriya S., Momiyama H., Satoh N., Takami S., Terashima Y., Suzuki O.,
RA   Nakagawa S., Senoh A., Mizoguchi H., Goto Y., Shimizu F., Wakebe H.,
RA   Hishigaki H., Watanabe T., Sugiyama A., Takemoto M., Kawakami B.,
RA   Yamazaki M., Watanabe K., Kumagai A., Itakura S., Fukuzumi Y.,
RA   Fujimori Y., Komiyama M., Tashiro H., Tanigami A., Fujiwara T.,
RA   Ono T., Yamada K., Fujii Y., Ozaki K., Hirao M., Ohmori Y.,
RA   Kawabata A., Hikiji T., Kobatake N., Inagaki H., Ikema Y., Okamoto S.,
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RA   Okitani R., Kawakami T., Noguchi S., Itoh T., Shigeta K., Senba T.,
RA   Matsumura K., Nakajima Y., Mizuno T., Morinaga M., Sasaki M.,
RA   Togashi T., Oyama M., Hata H., Watanabe M., Komatsu T.,
RA   Mizushima-Sugano J., Satoh T., Shirai Y., Takahashi Y., Nakagawa K.,
RA   Okumura K., Nagase T., Nomura N., Kikuchi H., Masuho Y., Yamashita R.,
RA   Nakai K., Yada T., Nakamura Y., Ohara O., Isogai T., Sugano S.;
RT   "Complete sequencing and characterization of 21,243 full-length human
RT   cDNAs.";
RL   Nat. Genet. 36:40-45(2004).
RN   [4]
RP   NUCLEOTIDE SEQUENCE [LARGE SCALE GENOMIC DNA].
RG   Human chromosome 11 international sequencing consortium;
RL   Submitted (NOV-2000) to the EMBL/GenBank/DDBJ databases.
CC   -!- SUBCELLULAR LOCATION: Membrane; single-pass type II membrane
CC       protein (Potential).
CC   -!- ALTERNATIVE PRODUCTS:
CC       Event=Alternative splicing; Named isoforms=4;
CC       Name=1; Synonyms=MSPL, Large form, Membrane-type;
CC         IsoId=Q9BYE2-1; Sequence=Displayed;
CC       Name=2;
CC         IsoId=Q9BYE2-2; Sequence=VSP_013103, VSP_013104;
CC         Note=No experimental confirmation available;
CC       Name=3; Synonyms=MSPS, Small form;
CC         IsoId=Q9BYE2-3; Sequence=VSP_013099, VSP_013102;
CC       Name=4;
CC         IsoId=Q9BYE2-4; Sequence=VSP_013100, VSP_013101;
CC         Note=No experimental confirmation available;
CC   -!- TISSUE SPECIFICITY: Isoform 1 and isoform 3 are predominantly
CC       expressed in lung, placenta, pancreas, and prostate. Isoform 3 is
CC       weakly expressed in testis and peripheral blood lymphocytes.
CC   -!- POLYMORPHISM: The repeat A-S-P-A-[GLQR] is polymorphic and the
CC       number of copies varies between 12 to 14.
CC   -!- SIMILARITY: Belongs to the peptidase S1 family.
CC   -!- SIMILARITY: Contains 1 LDL-receptor class A domain.
CC   -!- SIMILARITY: Contains 1 peptidase S1 domain.
CC   -!- SIMILARITY: Contains 1 SRCR domain.
CC   -!- CAUTION: Ref.2 has referred to this protein as TMPRSS6.
CC   ---------------------------------------------------------------------
CC   Copyrighted by the UniProt Consortium, see http://www.uniprot.org/terms
CC   Distributed under the Creative Commons Attribution-NoDerivs License
CC   ---------------------------------------------------------------------
DR   EMBL; AB048796; BAB39741.1; -; mRNA.
DR   EMBL; AB048797; BAB39742.1; -; mRNA.
DR   EMBL; AY190317; AAO38062.1; -; mRNA.
DR   EMBL; AK027798; BAB55376.1; -; mRNA.
DR   EMBL; AP002962; -; NOT_ANNOTATED_CDS; Genomic_DNA.
DR   HSSP; P00760; 1EZX.
DR   MEROPS; S01.087; -.
DR   Ensembl; ENSG00000137747; Homo sapiens.
DR   HGNC; HGNC:29808; TMPRSS13.
DR   GO; GO:0016021; C:integral to membrane; NAS.
DR   GO; GO:0004252; F:serine-type endopeptidase activity; NAS.
DR   GO; GO:0006508; P:proteolysis and peptidolysis; NAS.
DR   InterPro; IPR002172; LDL_rcpt_A.
DR   InterPro; IPR001254; Peptidase_S1_S6.
DR   InterPro; IPR001314; Peptidase_S1A.
DR   InterPro; IPR001190; Srcr_rcpt.
DR   Pfam; PF00057; Ldl_recept_a; 1.
DR   Pfam; PF00089; Trypsin; 1.
DR   PRINTS; PR00722; CHYMOTRYPSIN.
DR   SMART; SM00020; Tryp_SPc; 1.
DR   PROSITE; PS01209; LDLRA_1; FALSE_NEG.
DR   PROSITE; PS50068; LDLRA_2; FALSE_NEG.
DR   PROSITE; PS00420; SRCR_1; FALSE_NEG.
DR   PROSITE; PS50287; SRCR_2; 1.
DR   PROSITE; PS50240; TRYPSIN_DOM; 1.
DR   PROSITE; PS00134; TRYPSIN_HIS; 1.
DR   PROSITE; PS00135; TRYPSIN_SER; 1.
KW   Alternative splicing; Glycoprotein; Hydrolase; Membrane; Polymorphism;
KW   Protease; Repeat; Serine protease; Signal-anchor; Transmembrane.
FT   CHAIN         1    581       Transmembrane protease, serine 13.
FT                                /FTId=PRO_0000088698.
FT   TOPO_DOM      1    160       Cytoplasmic (Potential).
FT   TRANSMEM    161    181       Signal-anchor for type II membrane
FT                                protein (Potential).
FT   TOPO_DOM    182    581       Extracellular (Potential).
FT   REPEAT        9     13       1-1.
FT   REPEAT       14     18       2-1 (approximate).
FT   REPEAT       19     23       1-2.
FT   REPEAT       24     28       1-3.
FT   REPEAT       29     33       2-2.
FT   REPEAT       34     38       1-4.
FT   REPEAT       39     43       1-5.
FT   REPEAT       44     48       1-6.
FT   REPEAT       49     53       2-3.
FT   REPEAT       54     58       1-7.
FT   REPEAT       59     63       1-8.
FT   REPEAT       64     68       2-4.
FT   REPEAT       69     73       1-9 (approximate).
FT   REPEAT       74     78       1-10.
FT   REPEAT       79     83       1-11.
FT   REPEAT       84     88       1-12.
FT   DOMAIN      190    320       SRCR.
FT   DOMAIN      199    221       LDL-receptor class A.
FT   DOMAIN      321    554       Peptidase S1.
FT   REGION        9     88       12 x 5 AA repeats of A-S-P-A-[GLQR].
FT   REGION       14     68       4 x 5 AA repeats of T-P-P-G-R.
FT   COMPBIAS      9     89       Ala-rich.
FT   ACT_SITE    361    361       Charge relay system (By similarity).
FT   ACT_SITE    409    409       Charge relay system (By similarity).
FT   ACT_SITE    506    506       Charge relay system (By similarity).
FT   CARBOHYD    250    250       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD    287    287       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD    400    400       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD    440    440       N-linked (GlcNAc. . .) (Potential).
FT   DISULFID    245    309       By similarity.
FT   DISULFID    258    312       By similarity.
FT   DISULFID    346    362       By similarity.
FT   DISULFID    443    512       By similarity.
FT   DISULFID    475    491       By similarity.
FT   DISULFID    502    530       By similarity.
FT   VARSPLIC    146    181       GTSLPKFTWREGQKQLPLIGCVLLLIALVVSLIILF -> V
FT                                (in isoform 3).
FT                                /FTId=VSP_013099.
FT   VARSPLIC    423    486       AHIHPACLPMHGQTFSLNETCWITGFGKTRETDDKTSPFLR
FT                                EVQVNLIDFKKCNDYLVYDSYLT -> GEGICTPRSPAPQP
FT                                QHPLQPSHLSASVNSYPGPKASAGQKSKTLKDPYMEHFCFI
FT                                IRETEAQGL (in isoform 4).
FT                                /FTId=VSP_013100.
FT   VARSPLIC    487    581       Missing (in isoform 4).
FT                                /FTId=VSP_013101.
FT   VARSPLIC    555    581       VRSLQQDTAPSRLGTSSGGDPGGAPRV -> SEVRFRKS
FT                                (in isoform 3).
FT                                /FTId=VSP_013102.
FT   VARSPLIC    555    558       VRSL -> SSAG (in isoform 2).
FT                                /FTId=VSP_013103.
FT   VARSPLIC    559    581       Missing (in isoform 2).
FT                                /FTId=VSP_013104.
FT   CONFLICT    187    187       H -> Y (in Ref. 2).
FT   CONFLICT    192    192       Y -> H (in Ref. 1; BAB39741).
FT   CONFLICT    201    201       K -> E (in Ref. 2).
FT   CONFLICT    206    206       C -> R (in Ref. 2).
FT   CONFLICT    259    259       Q -> R (in Ref. 1).
FT   CONFLICT    298    298       E -> H (in Ref. 1).
FT   CONFLICT    496    496       H -> R (in Ref. 2).
SQ   SEQUENCE   581 AA;  62680 MW;  A4935CCCF31D29EE CRC64;

  Query Match             98.6%;  Score 2956;  DB 1;  Length 581;
  Best Local Similarity   99.8%;  Pred. No. 3.3e-156;
  Matches  553;  Conservative    0;  Mismatches    1;  Indels    0;  Gaps    0;

Qy          1 MERDSHGNASPARTPSAGASPAQASPAGTPPGRASPAQASPAQASPAGTPPGRASPAQAS 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MERDSHGNASPARTPSAGASPAQASPAGTPPGRASPAQASPAQASPAGTPPGRASPAQAS 60

Qy         61 PAGTPPGRASPGRASPAQASPARASPALASLSRSSSGRSSSARSASVTTSPTRVYLVRAT 120
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                 ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 PAGTPPGRASPGRASPAQASPARASPALASLSRSSSGRSSSARSASVTTSPTRVYLVRAT 120

Qy        121 PVGAVPIRSSPARSAPATRATRESPGTSLPKFTWREGQKQLPLIGCVLLLIALVVSLIIL 180
                 ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 PVGAVPIRSSPARSAPATRATRESPGTSLPKFTWREGQKQLPLIGCVLLLIALVVSLIIL 180

Qy        181 FQFWQGHTGIRYKEQRESCPKHAVRCDGVVDCKLKSDELGCVRFDWDKSLLKIYSGSSHQ 240
                 ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 FQFWQGHTGIRYKEQRESCPKHAVRCDGVVDCKLKSDELGCVRFDWDKSLLKIYSGSSHQ 240

Qy        241 WLPICSSNWNDSYSEKTCQQLGFESAHRTTEVAHRDFANSFSILRYNSTIQESLHRSECP 300
                 ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 WLPICSSNWNDSYSEKTCQQLGFESAHRTTEVAHRDFANSFSILRYNSTIQESLHRSECP 300

Qy        301 SQRYISLQCSHCGLRAMTGRIVGGALASDSKWPWQVSLHFGTTHICGGTLIDAQWVLTAA 360
                 ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 SQRYISLQCSHCGLRAMTGRIVGGALASDSKWPWQVSLHFGTTHICGGTLIDAQWVLTAA 360

Qy        361 HCFFVTREKVLEGWKVYAGTSNLHQLPEAASIAEIIINSNYTDEEDDYDIALMRLSKPLT 420
                 ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 HCFFVTREKVLEGWKVYAGTSNLHQLPEAASIAEIIINSNYTDEEDDYDIALMRLSKPLT 420

Qy        421 LSAHIHPACLPMHGQTFSLNETCWITGFGKTRETDDKTSPFLREVQVNLIDFKKCNDYLV 480
                 ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        421 LSAHIHPACLPMHGQTFSLNETCWITGFGKTRETDDKTSPFLREVQVNLIDFKKCNDYLV 480

Qy        481 YDSYLTPRMMCAGDLRGGRDSCQGDSGGPLVCEQNNRWYLAGVTSWGTGCGQRNKPGVYT 540
                 |||||||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||
Db        481 YDSYLTPRMMCAGDLHGGRDSCQGDSGGPLVCEQNNRWYLAGVTSWGTGCGQRNKPGVYT 540

Qy        541 KVTEVLPWIYSKME 554
                 ||||||||||||||
Db        541 KVTEVLPWIYSKME 554
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RESULT 2
TMPSD_MOUSE
ID   TMPSD_MOUSE    STANDARD;      PRT;   543 AA.
AC   Q5U405; Q8CFE0; Q91VQ8;
DT   15-MAR-2005, integrated into UniProtKB/Swiss-Prot.
DT   15-MAR-2005, sequence version 2.
DT   07-MAR-2006, entry version 16.
DE   Transmembrane protease, serine 13 (EC 3.4.21.-) (Mosaic serine
DE   protease) (Membrane-type mosaic serine protease).
GN   Name=Tmprss13; Synonyms=Msp;
OS   Mus musculus (Mouse).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Euarchontoglires; Glires; Rodentia; Sciurognathi;
OC   Muroidea; Muridae; Murinae; Mus.
OX   NCBI_TaxID=10090;
RN   [1]
RP   NUCLEOTIDE SEQUENCE [LARGE SCALE MRNA].
RC   STRAIN=B5/EGFP, and FVB/N;
RC   TISSUE=Mammary tumor, and Trophoblast stem cell;
RX   MEDLINE=22388257; PubMed=12477932; DOI=10.1073/pnas.242603899;
RA   Strausberg R.L., Feingold E.A., Grouse L.H., Derge J.G.,
RA   Klausner R.D., Collins F.S., Wagner L., Shenmen C.M., Schuler G.D.,
RA   Altschul S.F., Zeeberg B., Buetow K.H., Schaefer C.F., Bhat N.K.,
RA   Hopkins R.F., Jordan H., Moore T., Max S.I., Wang J., Hsieh F.,
RA   Diatchenko L., Marusina K., Farmer A.A., Rubin G.M., Hong L.,
RA   Stapleton M., Soares M.B., Bonaldo M.F., Casavant T.L., Scheetz T.E.,
RA   Brownstein M.J., Usdin T.B., Toshiyuki S., Carninci P., Prange C.,
RA   Raha S.S., Loquellano N.A., Peters G.J., Abramson R.D., Mullahy S.J.,
RA   Bosak S.A., McEwan P.J., McKernan K.J., Malek J.A., Gunaratne P.H.,
RA   Richards S., Worley K.C., Hale S., Garcia A.M., Gay L.J., Hulyk S.W.,
RA   Villalon D.K., Muzny D.M., Sodergren E.J., Lu X., Gibbs R.A.,
RA   Fahey J., Helton E., Ketteman M., Madan A., Rodrigues S., Sanchez A.,
RA   Whiting M., Madan A., Young A.C., Shevchenko Y., Bouffard G.G.,
RA   Blakesley R.W., Touchman J.W., Green E.D., Dickson M.C.,
RA   Rodriguez A.C., Grimwood J., Schmutz J., Myers R.M.,
RA   Butterfield Y.S.N., Krzywinski M.I., Skalska U., Smailus D.E.,
RA   Schnerch A., Schein J.E., Jones S.J.M., Marra M.A.;
RT   "Generation and initial analysis of more than 15,000 full-length human
RT   and mouse cDNA sequences.";
RL   Proc. Natl. Acad. Sci. U.S.A. 99:16899-16903(2002).
CC   -!- SUBCELLULAR LOCATION: Membrane; single-pass type II membrane
CC       protein (Potential).
CC   -!- SIMILARITY: Belongs to the peptidase S1 family.
CC   -!- SIMILARITY: Contains 1 LDL-receptor class A domain.
CC   -!- SIMILARITY: Contains 1 peptidase S1 domain.
CC   -!- SIMILARITY: Contains 1 SRCR domain.
CC   ---------------------------------------------------------------------
CC   Copyrighted by the UniProt Consortium, see http://www.uniprot.org/terms
CC   Distributed under the Creative Commons Attribution-NoDerivs License
CC   ---------------------------------------------------------------------
DR   EMBL; BC010843; AAH10843.1; -; mRNA.
DR   EMBL; BC042878; AAH42878.1; -; mRNA.
DR   EMBL; BC085323; AAH85323.1; -; mRNA.
DR   HSSP; P00760; 1EZX.
DR   MEROPS; S01.087; -.
DR   MGI; MGI:2682935; Tmprss13.
DR   InterPro; IPR002172; LDL_rcpt_A.
DR   InterPro; IPR001254; Peptidase_S1_S6.
DR   InterPro; IPR001314; Peptidase_S1A.
DR   InterPro; IPR001190; Srcr_rcpt.
DR   Pfam; PF00057; Ldl_recept_a; 1.
DR   Pfam; PF00530; SRCR; 1.
DR   Pfam; PF00089; Trypsin; 1.
DR   PRINTS; PR00722; CHYMOTRYPSIN.
DR   SMART; SM00202; SR; 1.
DR   SMART; SM00020; Tryp_SPc; 1.
DR   PROSITE; PS01209; LDLRA_1; FALSE_NEG.
DR   PROSITE; PS50068; LDLRA_2; FALSE_NEG.
DR   PROSITE; PS00420; SRCR_1; FALSE_NEG.
DR   PROSITE; PS50287; SRCR_2; 1.
DR   PROSITE; PS50240; TRYPSIN_DOM; 1.
DR   PROSITE; PS00134; TRYPSIN_HIS; 1.
DR   PROSITE; PS00135; TRYPSIN_SER; 1.
KW   Glycoprotein; Hydrolase; Membrane; Protease; Repeat; Serine protease;
KW   Signal-anchor; Transmembrane.
FT   CHAIN         1    543       Transmembrane protease, serine 13.
FT                                /FTId=PRO_0000088699.
FT   TOPO_DOM      1    143       Cytoplasmic (Potential).
FT   TRANSMEM    144    164       Signal-anchor for type II membrane
FT                                protein (Potential).
FT   TOPO_DOM    165    543       Extracellular (Potential).
FT   REPEAT       14     17       1-1.
FT   REPEAT       18     22       2-1.
FT   REPEAT       23     27       2-2 (approximate).
FT   REPEAT       28     31       1-2 (approximate).
FT   REPEAT       32     36       2-3.
FT   REPEAT       37     40       1-3.
FT   REPEAT       41     45       2-4.
FT   REPEAT       46     49       1-4.
FT   REPEAT       50     54       2-5.
FT   REPEAT       55     59       2-6 (approximate).
FT   REPEAT       60     64       2-7.
FT   REPEAT       65     69       2-8.
FT   DOMAIN      180    202       LDL-receptor class A.
FT   DOMAIN      199    301       SRCR.
FT   DOMAIN      302    535       Peptidase S1.
FT   REGION       14     49       4 x 4 AA repeats of T-P-P-Q.
FT   REGION       18     69       1-8 x 5 AA repeats of A-S-P-A-R.
FT   COMPBIAS     11     72       Pro-rich.
FT   ACT_SITE    342    342       Charge relay system (By similarity).
FT   ACT_SITE    390    390       Charge relay system (By similarity).
FT   ACT_SITE    487    487       Charge relay system (By similarity).
FT   CARBOHYD    231    231       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD    268    268       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD    381    381       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD    421    421       N-linked (GlcNAc. . .) (Potential).
FT   DISULFID    226    290       By similarity.
FT   DISULFID    239    293       By similarity.
FT   DISULFID    327    343       By similarity.
FT   DISULFID    424    493       By similarity.
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FT   DISULFID    456    472       By similarity.
FT   DISULFID    483    511       By similarity.
FT   CONFLICT    281    281       S -> P (in Ref. 1; AAH42878).
FT   CONFLICT    475    475       D -> G (in Ref. 1; AAH85323).
FT   CONFLICT    530    530       I -> T (in Ref. 1; AAH85323).
SQ   SEQUENCE   543 AA;  59806 MW;  61026D04A0FCE2D5 CRC64;

  Query Match             83.7%;  Score 2510.5;  DB 1;  Length 543;
  Best Local Similarity   83.3%;  Pred. No. 1.7e-131;
  Matches  468;  Conservative   40;  Mismatches   35;  Indels   19;  Gaps    4;

Qy          1 MERDSHGNASPARTPSAGASPAQASPAGTPPGRASPAQASPAQASPAGTPPGRASPAQAS 60
              |:| || |:|||||      | ||||| | | ||      | ||||| |||      |||
Db          1 MDRGSHRNSSPART------PPQASPARTSPARA------PPQASPARTPP------QAS 42

Qy         61 PAGTPPGRASPGRASPAQASPARASPALASLSRSSSGRSSSARSASVTTSPTRVYLVRAT 120
              || ||| :||| || | |||||||||| |  ||||||||||||||| |:||||||||||
Db         43 PARTPP-QASPARAPPPQASPARASPARAPPSRSSSGRSSSARSASTTSSPTRVYLVRAT 101

Qy        121 PVGAVPIRSSPARSAPATRATRESPGTSLPKFTWREGQKQLPLIGCVLLLIALVVSLIIL 180
              ||||||||:||||||||||||||||| | |||:|:| |:||||||||:|||:||:|||:|
Db        102 PVGAVPIRASPARSAPATRATRESPGLSFPKFSWQETQRQLPLIGCVILLISLVISLILL 161

Qy        181 FQFWQGHTGIRYKEQRESCPKHAVRCDGVVDCKLKSDELGCVRFDWDKSLLKIYSGSSHQ 240
              | ||:|||||:|||  |||| ||||||||||||:|||||||||||||||||:|||||:
Db        162 FYFWRGHTGIKYKEPLESCPIHAVRCDGVVDCKMKSDELGCVRFDWDKSLLKVYSGSSGE 221

Qy        241 WLPICSSNWNDSYSEKTCQQLGFESAHRTTEVAHRDFANSFSILRYNSTIQESLHRSECP 300
              |||:|||:|||: |::|||||||:||:|||||||  :|| :  ||:|||||:||:|
Db        222 WLPVCSSSWNDTDSKRTCQQLGFDSAYRTTEVAHRDITSSFLLSEYNTTIQESLYRSQCS 281

Qy        301 SQRYISLQCSHCGLRAMTGRIVGGALASDSKWPWQVSLHFGTTHICGGTLIDAQWVLTAA 360
              |:||:|||||||||||||||||||| |:|||||||||||||||||||||||||||||||
Db        282 SRRYVSLQCSHCGLRAMTGRIVGGALTSESKWPWQVSLHFGTTHICGGTLIDAQWVLTAA 341

Qy        361 HCFFVTREKVLEGWKVYAGTSNLHQLPEAASIAEIIINSNYTDEEDDYDIALMRLSKPLT 420
              |||||||||:|||||||||||||||||||||::|||| |||||:|||||||:|||||||
Db        342 HCFFVTREKLLEGWKVYAGTSNLHQLPEAASISQIIINGNYTDEQDDYDIALIRLSKPLT 401

Qy        421 LSAHIHPACLPMHGQTFSLNETCWITGFGKTRETDDKTSPFLREVQVNLIDFKKCNDYLV 480
              |||||||||||||||| ||||||||||||:|||:|||||||||||||||||||||||||
Db        402 LSAHIHPACLPMHGQTFGLNETCWITGFGKTKETDEKTSPFLREVQVNLIDFKKCNDYLV 461

Qy        481 YDSYLTPRMMCAGDLRGGRDSCQGDSGGPLVCEQNNRWYLAGVTSWGTGCGQRNKPGVYT 540
              |||||||||||||||||||||||||||||||||||||||||||||||||||:|||||||
Db        462 YDSYLTPRMMCAGDLRGGRDSCQGDSGGPLVCEQNNRWYLAGVTSWGTGCGQKNKPGVYT 521

Qy        541 KVTEVLPWIYSKMESEVRFRKS 562
              |||||||||| ||||||||||
Db        522 KVTEVLPWIYRKMESEVRFRKS 543


RESULT 3
Q4SPG0_TETNG
ID   Q4SPG0_TETNG   PRELIMINARY;   PRT;   359 AA.
AC   Q4SPG0;
DT   19-JUL-2005, integrated into UniProtKB/TrEMBL.
DT   19-JUL-2005, sequence version 1.
DT   07-FEB-2006, entry version 4.
DE   Chromosome 16 SCAF14537, whole genome shotgun sequence. (Fragment).
GN   ORFNames=GSTENG00014849001;
OS   Tetraodon nigroviridis (Green puffer).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Actinopterygii; Neopterygii; Teleostei; Euteleostei; Neoteleostei;
OC   Acanthomorpha; Acanthopterygii; Percomorpha; Tetraodontiformes;
OC   Tetradontoidea; Tetraodontidae; Tetraodon.
OX   NCBI_TaxID=99883;
RN   [1]
RP   NUCLEOTIDE SEQUENCE.
RX   PubMed=15496914; DOI=10.1038/nature03025;
RA   Jaillon O., Aury J.-M., Brunet F., Petit J.-L., Stange-Thomann N.,
RA   Mauceli E., Bouneau L., Fischer C., Ozouf-Costaz C., Bernot A.,
RA   Nicaud S., Jaffe D., Fisher S., Lutfalla G., Dossat C., Segurens B.,
RA   Dasilva C., Salanoubat M., Levy M., Boudet N., Castellano S.,
RA   Anthouard V., Jubin C., Castelli V., Katinka M., Vacherie B.,
RA   Biemont C., Skalli Z., Cattolico L., Poulain J., De Berardinis V.,
RA   Cruaud C., Duprat S., Brottier P., Coutanceau J.-P., Gouzy J.,
RA   Parra G., Lardier G., Chapple C., McKernan K.J., McEwan P., Bosak S.,
RA   Kellis M., Volff J.-N., Guigo R., Zody M.C., Mesirov J.,
RA   Lindblad-Toh K., Birren B., Nusbaum C., Kahn D., Robinson-Rechavi M.,
RA   Laudet V., Schachter V., Quetier F., Saurin W., Scarpelli C.,
RA   Wincker P., Lander E.S., Weissenbach J., Roest Crollius H.;
RT   "Genome duplication in the teleost fish Tetraodon nigroviridis reveals
RT   the early vertebrate proto-karyotype.";
RL   Nature 431:946-957(2004).
RN   [2]
RP   NUCLEOTIDE SEQUENCE.
RG   Genoscope; Whitehead Institute Centre for Genome Research;
RL   Submitted (FEB-2004) to the EMBL/GenBank/DDBJ databases.
CC   -!- CAUTION: The sequence shown here is derived from an
CC       EMBL/GenBank/DDBJ whole genome shotgun (WGS) entry which is
CC       preliminary data.
CC   ---------------------------------------------------------------------
CC   Copyrighted by the UniProt Consortium, see http://www.uniprot.org/terms
CC   Distributed under the Creative Commons Attribution-NoDerivs License
CC   ---------------------------------------------------------------------
DR   EMBL; CAAE01014537; CAF97472.1; -; Genomic_DNA.
DR   GO; GO:0016020; C:membrane; IEA.
DR   GO; GO:0005044; F:scavenger receptor activity; IEA.
DR   GO; GO:0004252; F:serine-type endopeptidase activity; IEA.
DR   GO; GO:0006508; P:proteolysis; IEA.
DR   InterPro; IPR001254; Peptidase_S1_S6.
DR   InterPro; IPR001314; Peptidase_S1A.
DR   InterPro; IPR001190; Srcr_rcpt.
DR   Pfam; PF00089; Trypsin; 1.
DR   PRINTS; PR00722; CHYMOTRYPSIN.
DR   SMART; SM00020; Tryp_SPc; 1.
DR   PROSITE; PS50240; TRYPSIN_DOM; 1.
DR   PROSITE; PS00134; TRYPSIN_HIS; UNKNOWN_1.
DR   PROSITE; PS00135; TRYPSIN_SER; 1.
FT   NON_TER       1      1
FT   NON_TER     359    359
SQ   SEQUENCE   359 AA;  38943 MW;  4C14083C78233B37 CRC64;

  Query Match             29.7%;  Score 891;  DB 2;  Length 359;
  Best Local Similarity   44.2%;  Pred. No. 1.1e-41;
  Matches  159;  Conservative   70;  Mismatches  121;  Indels   10;  Gaps    4;

Qy        202 HAVRCDGVVDCKLKSDELGCVRFDWDKSLLKIYSGSSHQWLPICSSNWNDSYSEKTCQQL 261
              :|  |||| || | |||  ||     | ::|:: :    ::||:| : |::| :::|| :|
Db          1 NATHCDGVRDCTLGSDETACVMLGND-NILQVKTSQDGRFLPVCYNGWDESLAKETCTKL 59

Qy        262 GFESAHRTTEVAHRDFANSFSILRYNSTIQESLH-----RSECPSQRYISLQCSHCGLRA 316
              || : : |      :     |   | ||      |        | || |: ::|||  || |
Db         60 GFRNFYATNPSTSQ--PKSSPTLTINSRSSPYLQGRVNVSSSCPGQQTVALQCLDCGQRR 117

Qy        317 MTGRIVGGALASDSKWPWQVSLHFGTTHICGGTLIDAQWVLTAAHCFFVTREKVL--EGW 374
              | ||:|| :|   :||||::|||  :|:||| ||   :||||||||  : :  :  | |
Db        118 STSRIIGGNVAKLGQWPWQMTLHFRGSHVCGGILISPDFVLTAAHCFPESNKLAILAENW 177

Qy        375 KVYAGTSNLHQLPEAASIAEIIINSNYTDEEDDYDIALMRLSKPLTLSAHIHPACLPMHG 434
              :||:|  :| :||:   :  |::: |  : :|||:||::|: |:    :: |||||
Db        178 EVYSGVESLDKLPKPYKVKRILLSELYNSDTNDYDVALLKLAAPVVFDDNVQPACLPSRD 237

Qy        435 QTFSLNETCWITGFGKTRETDDKTSPFLREVQVNLIDFKKCNDYLVYDSYLTPRMMCAGD 494
              |  :    || |||| | :      |  | || ||:|    ||   ||: :|  |:||||
Db        238 QILAPGTQCWTTGFGTTEDGSSSVSKSLMEVSVNIISDTVCNSVTVYNKAVTKNMLCAGD 297

Qy        495 LRGGRDSCQGDSGGPLVCEQNNRWYLAGVTSWGTGCGQRNKPGVYTKVTEVLPWIYSKME 554
              |:||:|||||||||||:::::|||: |:||||:|||| |||||||:|: |||||||:|:
Db        298 LKGGKDSCQGDSGGPLVCQEDDRWYVVGITSWGSGCGQANKPGVYTRVSSVLPWIYSRMQ 357


RESULT 4
TMPS2_MOUSE
ID   TMPS2_MOUSE    STANDARD;      PRT;   490 AA.
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